幽门螺杆菌相关胃外疾病研究进展

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Research progress of Helicobacter pylori related extra-gastric diseases

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Abstract： Helicobacter pylori (Hp) is a common gram-negative bacterium in gastrointestinal tract infection. It mainly exists on the surface of gastric epithelial cells and mucus, and is related to gastric ulcer, gastric cancer and gastric mucosa associated lymphoma. Some studies have shown that helicobacter pylori may induce or aggravate some extra-gastric diseases. Recently, other studies have reported that helicobacter pylori is associated with novel coronavirus pneumonia; It indirectly or directly participates in the occurrence and development of diseases by stimulating the body to produce inflammatory factors or cross immune response. In addition, Helicobacter pylori can also enter the Candida, release toxins to participate in extra-gastric diseases and evade the immune system and drug effects. This paper summarizes the research reports on helicobacter pylori related extra-gastric diseases abroad in recent years, aiming to arouse the attention of clinical workers to helicobacter pylori related extra-gastric diseases, popularize their relevant knowledge, and avoid the aggravation of helicobacter pylori or other diseases.

Key words： Helicobacter pylori; extra-gastric diseases; Cross immune response; Novel coronavirus pneumonia

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【摘 要】 幽门螺杆菌(*Helicobacter pylori*，Hp)是一种常见的胃肠道感染的革兰阴性杆菌，它主要存在于胃上皮细胞表面和黏液中，与胃溃疡、胃癌和胃黏膜相关淋巴瘤有关。有研究表明幽门螺杆可能诱发或加重某些胃外疾病，近日还有研究报道了幽门螺杆菌与新型冠状病毒肺炎有关；其通过刺激机体产生炎症因子或交叉免疫反应间接或直接的参与疾病的发生和发展。此外幽门螺杆菌还可进入念珠菌内，释放毒素参与胃外疾病并躲避免疫系统和药物作用。本文总结近几年国外对幽门螺杆菌相关胃外疾病的研究报道，旨在引起临床工作者对幽门螺杆菌相关胃外疾病的重视、普及其相关学科知识，避免幽门螺杆菌加重或诱发其他疾病。

【关 键 词】幽门螺杆菌；胃外疾病；交叉免疫反应；新型冠状病毒肺炎

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幽门螺杆菌在全球范围内的感染率超过 50%[1]，尤其是在发展中国家的感染率会明显高于发达国家的感染率[2]。除了胃内疾病，越来越多的证据表明，幽门螺杆菌的感染与心血管系统[3]、免疫系统[4]和神经系统[5、6]等系统疾病相关，近日还有研究报道了幽门螺杆菌与新型冠状病毒肺炎有关[7]。由于幽门螺杆菌的感染使得治疗某些疾病较为复杂，并且医务工作者在患者感染幽门螺杆菌早期忽略了其与某些胃外疾病的相关性，使得患者原有某些疾病加重。

幽门螺杆菌是一种革兰阴性杆菌，菌体呈螺旋形。幽门螺杆菌致病性与其鞭毛、黏附素、细胞毒素相关蛋白 CagA 和空泡毒素相关蛋白 VacA[8]有关，其中 CagA 蛋白是其最有代表性的毒力因子，系一种由 *cag* 致病岛 *cagA* 基因编码、分子量约为 140kDa 的免疫显性蛋白[9]。这些毒力因子有些可诱直接对机体产生损害，有些可诱导机体炎症反应，使体内炎症因子增多从而导致某些疾病，例如：CagA 可刺激机体使白细胞介素 IL-6 和肿瘤坏死因子增多，促进甲状腺细胞的凋亡，诱发甲状腺疾病[10]。故在治疗幽门螺杆菌时，中和其分泌的某些毒素也应当纳入临床治疗的考量。

近日有研究指出：Hp 能与念珠菌形成原核-真核共生物[11]，例如 Hp 内化念珠菌，在念珠菌内的 Hp 可持续释放毒力因子于胞外，并且躲避抗生素的作用[12]，从而对患者机体产生持续的影响。此外部分 Hp 感染者无明显症状[13]，得不到及时的治疗，使得 Hp 持续产生毒力因子对胃外疾病产生影响。因此，本文总结了与幽门螺杆菌相关的部分胃外疾病，简述发生机制，旨在打开幽门螺杆菌治疗的的临床思路，揭示对幽门螺杆菌某些毒力因子干预的重要性。

1. 呼吸系统疾病

1.1 肺癌

肺癌是我国死亡率最高的癌症，通常可分为非小细胞肺癌（non-small cell lung cancer，NSCLC)和小细胞肺癌（small cell lung cancer，SCLC），肺癌的病因至今仍不明朗。最近有研究报道了某些病原微生物与肺癌有关——幽门螺杆菌[14]。来自我国北京的一项数据表明：幽门螺杆菌的感染与某些肿瘤标志物水平有关，在感染幽门螺杆菌的肺癌患者中，其癌胚抗原 CEA 水平更高，而甲胎蛋白 AFP 和 CA724 会偏低[15]。CEA 水平的升高可间接反应癌症的进展或复发，因此我们有理由认为幽门螺杆菌有可能在某些特定的癌症中发挥作用，同时也为临床提供思路：对于感染幽门螺杆菌的患者，应重视肿瘤标记物水平可受其影响，在评估患者癌症进展程度和治疗过程中是否将幽门螺杆菌纳入整体系统考量？对待此类患者，国际上有研究发现了一些“量体裁衣”的药物，例如：生物相容性银纳米颗粒[16]：即可靶向破坏肺癌细胞，又可抑制幽门螺杆菌。还有研究指出幽门螺杆菌的感染会使接受免疫治疗的非小细胞肺癌患者体内干扰素和白细胞介素-6 表达显著降低，影响癌症患者免疫治疗的疗效，关于这点考虑与幽门螺杆菌毒理因子 VacA 抑制骨髓细胞活性有关[17]。上述研究表明：1）中和幽门螺杆菌毒素与根治幽门螺杆菌同样重要。2）幽门螺杆菌血清学检查可纳入评估免疫治疗对非小细胞肺癌的预期疗效。3）这个观点可进一步研究，有助于扩大到其他肿瘤，评估治疗疗效。

1.2 新型冠状病毒肺炎

新型冠状病毒 COVID-19 被认为是最致命流行病之一，其通过结合血管紧张素转化酶-2（angiotensin-converting enzyme-2，ACE-2）受体进入细胞[18]，从而导致以呼吸系统为主的一系列临床症状。有研究指出幽门螺杆菌可上调机体肠道细胞 ACE-2 受体的表导，导致更多的病毒进入细胞，使得这类患者消化道

症状例如：腹痛、腹泻相较未感染人群更重[19]。此外，幽门螺杆菌还可刺激机体产生大量炎症介质，**如**：肿瘤坏死因子-a 和白细胞介素-8 **等**，这些炎症因子与病毒一同介导急性肺损伤[20]。除了感染阶段，来自《*Gut*》的一项研究表明治疗幽门螺杆菌阶段质子泵抑制剂的使用会增大 COVID-19 的易感性[21]，还与患者严重临床症状有关，这可能与质子泵抑制剂会增加嗜铬粒蛋白 A（chromogranin A，CgA）

血浆水平有关[22]。CgA 水平可作为早期预测新冠患者死亡的独立因子[23]，这也说明 CgA 在新冠患者中的潜在作用。

2. 神经系统疾病

2.1 阿尔兹海默症

由于幽门螺杆菌不直接侵犯神经系统，所以早年医学研究忽略了幽门螺杆菌在神经系统疾病中的作用。阿尔兹海默症（Alzheimer’s disease,AD)是一种神经系统退行性疾病,其特点是大脑皮层和皮层下区域神经元丢失。近几年有学者开始研究 AD 与病原微生物感染的关系[24]，幽门螺杆菌感染也逐渐考虑为其病因[25]。

有学者认为，幽门螺杆菌与 AD 存在明确关联[26]，关于其机制推测如下：1）革兰阴性细菌释放的外膜囊泡可携带毒理因子[27]，而幽门螺杆菌的外膜囊泡可通过血脑屏障，诱导神经胶质细胞的激活和神经元功能的障碍，加速 AD 的形成。2）幽门螺杆菌的脲酶具有促炎活性和激活免疫系统的能力，从而诱发神经系统的炎症和神经系统退行性变的发生[28]。3）幽门螺杆菌可导致患者肠道黏膜的通透性增加、肠道菌群异常从而成为诱发 AD 的关键启动因素[29]。

2.2 其他神经系统疾病

幽门螺杆菌与神经系统其他疾病的关系及可能机制如下表 1：

表 1 幽门螺杆菌与神经系统疾病的关系

Table 1 Relationship between helicobacter pylori and nervous system disease

Disease name	Analysis of Pathophysiological Mechanisms
Parkinsonism[30-32]	Helicobacter pylori can inhibit the absorption of levodopa in the treatment of Parkinson's disease, resulting in a decrease in drug concentration in the plasma[33]。

multiple sclerosis[34-35]	It may be related to Hp induced cellular and humoral immune response[35]。
migraine[36-37]	It may be related to Helicobacter pylori stimulating the release of inflammatory mediators and disrupting the gut microbiota[37]。

2.3 幽门螺杆菌的治疗对神经系统疾病的意义

这些与幽门螺杆菌相关神经系统疾病都在表明：幽门螺杆菌的感染所导致的疾病已不仅局限于胃内或消化系统内，神经系统疾病大部风病因不明，但幽门螺杆菌却被报道广泛。上述报道中，也揭示了幽门螺杆菌治疗在神经系统疾病中的重要性：1）幽门螺杆菌的外膜囊泡是在其感染三周以后才测到[27]，表明早期检测和根治幽门螺杆菌的重要性；2）从上述研究中可以看出肠道菌群对神经系统的意义，有学者形象的将二者关系称之为脑肠轴[38]—肠道神经系统与中枢神经系统通过多边机制相互联系，其中也包括肠道微生物的参与，而幽门螺杆菌可影响肠道原有菌群[39]。故学者提出益生菌治疗神经系统疾病是否有效的假设[40]？而这一假设也得到了研究证实，例如：长期口服益生菌的小鼠可有效延缓 AD 的进展，而益生菌的服用同样有助于减少幽门螺杆菌所带来的副作用[41]。

3. 生殖系统疾病

3.1 妊娠剧吐

妊娠剧吐是一种由于妊娠期间孕激素水平发生变化而导致孕妇出现恶心和呕吐为主一系列临床症状的疾病。有学者发现幽门螺杆菌与妊娠剧吐有关[42]。另一项研究通过对患者进行羊水穿刺，检测到羊水当中存在幽门螺杆菌特异性抗原[43]，检测出幽门螺杆菌感染羊水的患者相较阴性对照组，出现妊娠剧吐的发病率更高。这项研究有助于拓宽临床检测幽门螺杆菌的思路，并且有研究指出妊娠期感染幽门螺杆菌对胎儿发育（例如：双顶径小、体重低和头围小）有着明确影响[44]，表明羊水中检测到幽门螺杆菌时应尽早根治，避免给母体及胎儿带来的双重影响。虽然羊水检测能更直接说明宫腔内可能存在幽门螺杆菌，但这项研究未评估羊水检测和粪便检测阳性率对比，并且若粪便检测阳性患者羊水中同样存在幽门螺杆菌抗原，则患者和医务人员更倾向于无创检查。

3.2 男性不育

男性不育发病机制复杂[45]，迄今为止仍有大量患者病因不明[46]。近几年，有国外学者认为幽门螺杆菌的感染与男性不育有关[47],在幽门螺杆菌感染的人群中精子活力、浓度和生育指数都有降低[48]。有学者发现感染了幽门螺杆菌的去雄治疗前列腺癌患者其死亡率降低，推测幽门螺杆菌可能影响男性体内雄激素水平[49]。还有研究发现精子鞭毛的主要成分微管蛋白与幽门螺杆菌的鞭毛蛋白、CagA 和 VacA 存在部分结构同源性，这表明幽门螺杆菌有可能刺激人体产生交叉免疫[50]，诱导机体产生抗精子抗体使患者精子质量下降。

3.3 特殊人群幽门螺杆菌治疗

鉴于妊娠期幽门螺杆菌对胎儿及母体的影响，早期检测并根治幽门螺杆菌尤为重要。幽门螺杆菌的治疗目前推荐的是两种抗生素+质子泵抑制剂+铋剂，但妊娠期的特殊性，抗生素使用需更加小心，除了已知药物透过胎盘屏障对胎儿造成影响，某些抗生素妊娠期服用还会造成母乳中 IgG 含量下降，降低新生儿抵抗力[51]。此外，质子泵抑制剂的使用同样有增大妊娠期女性先兆子痫、妊娠糖尿病[52]的风险。有体外实验表明：泮托拉唑可增加精子蛋白质磷酸化和阻止精子细胞膜电位超极化从而抑制精子获能[53]，埃索美拉唑作为新一代的 PPI，有研究发现在服用 60min 后，减少了活动精子的总数[54]。综上，特殊人群的幽门螺杆菌治疗同样较为特殊，建议可推广服用益生菌辅助治疗，理由如下：1）妊娠期服用益生菌，可降低先兆子痫、妊娠期糖尿病的发病率[55]。2）男性不育患者服用益生菌，可通过改善肠道菌群，起到提高精液质量、辅助治疗男性不育的作用[56]。3）益生菌的使用可增强抗生素疗效、减少幽门螺杆菌复发的可能性[57]。

4. 关于幽门螺杆菌其他研究进展

4.1 幽门螺杆菌传播途径

幽门螺杆菌的传统传播途径被认为是粪-口与口-口两种[58]，但早在 2008 年便有学者提出：幽门螺杆菌是否通过性传播的假设[59],有研究发现幽门螺杆菌在性伴侣之间的患病率明显高于对照组[60]，推测幽门螺杆菌可通过性传播，理由如下：1）在口腔中发现了幽门螺杆菌[61、62]，表明其可生活在口腔环境中。2）在女性阴道中同样发现了幽门螺杆菌毒力基因[63]。综上，幽门螺杆菌有可能通过性传播，甚至是母婴垂直传播，明确幽门螺杆菌具体传播途径，有助于科学

防治幽门螺杆菌、减少幽门螺杆菌胃外疾病的发生。但上述结论仍存在不足，例如：性伴侣之间患病率更高[60]的研究中，仅测定阳性率并未确定配偶之间幽门螺杆菌的同源性。但至少有一点可以确认：幽门螺杆菌容易以家庭为单位，在家族成员中传播[64]，在此建议，基于幽门螺杆菌传播途径多样性，其筛查和防治同样应以家庭为单位。

4.2 幽门螺杆菌形成真核-原核共生物

念珠菌是一种生活在女性阴道的真菌，幽门螺杆菌作为唯一一种生活在胃内的细菌，很难将二者联想到一起，但近日有学者从女性阴道分泌物中的念珠菌内检测到了幽门螺杆菌的特异性核酸[65]，体外实验也同样发现幽门螺杆菌为躲避不利条件会进入念珠菌:胃内的幽门螺杆菌可催化尿素产生氨气降低胃内的酸性,而阴道中尿素含量低,幽门螺杆菌为躲避不利因素，可进入念珠菌内形成真核-原核共生物[65-67]即幽门螺杆菌内化念珠菌，念珠菌还可增强细菌的致病性[68]。而念珠菌内的幽门螺杆菌同样可释放 CagA 与念珠菌之外，表明其仍有可能产生毒力因子引起胃外疾病(详见图一)。故建议，幽门螺杆菌的根治与筛查不应只局限于胃内，还应破坏其共生物。有研究发现念珠菌在缺乏营养的情况下其细胞壁发生改变[66]，Hp 难以进入，这为杜绝 Hp 内化念珠菌的形成提供新的思路。

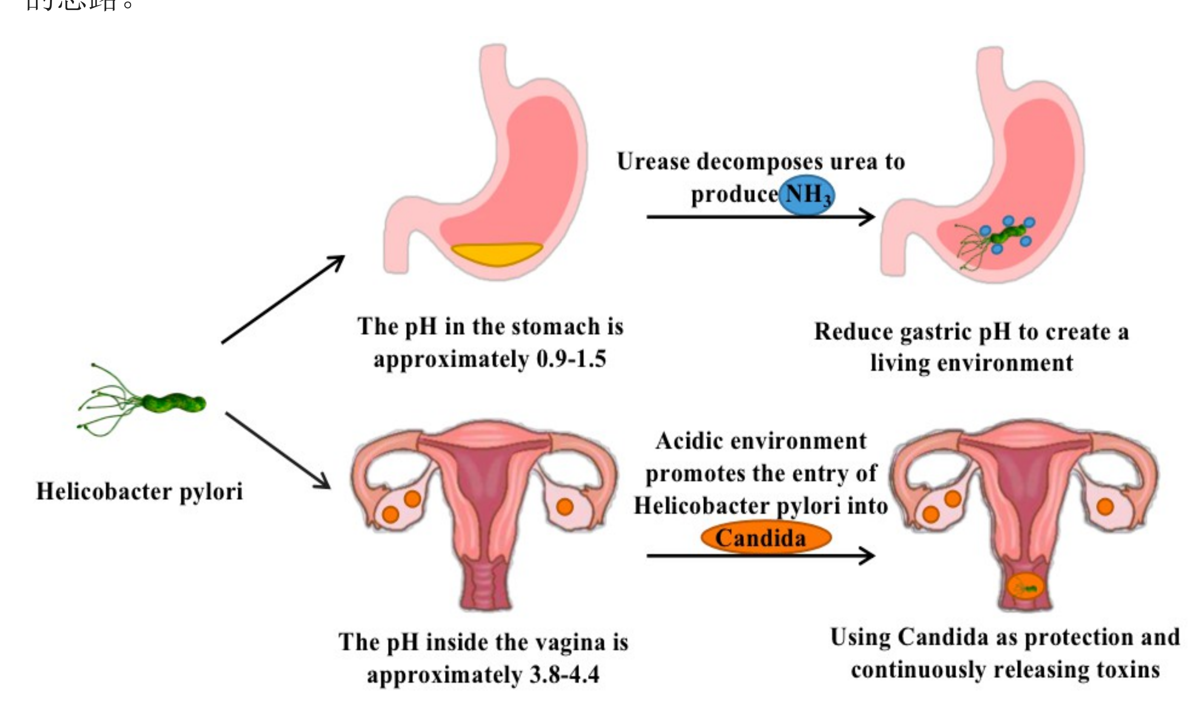


图 1 幽门螺杆菌可形成真核-原核共生物

Fig.1 Helicobacter pylori can form eukaryotic prokaryotic co-organisms

5. 总结和展望

近几年有大量有大量研究证据表明，幽门螺杆菌感染人体后出现各种复杂表现，并且与许多系统疾病都有关联。依据本文中总结的呼吸系统、神经系统和生殖系统等可以看出，幽门螺杆菌无需直接侵入该系统，甚至是念珠菌内的幽门螺杆菌亦可释放毒力因子，其可通过毒力因子和交叉抗原造成胃外系统的疾病，表明幽门螺杆菌的治疗和筛查应综合考量。但由于幽门螺杆菌存在众多亚型，明确各亚型与不同疾病之间的关联和治疗，应作为下一步幽门螺杆菌的研究重点。

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